23

**INHIBITION BY GALANIN OF $5HT_2$ RECEPTOR MEDIATED PI HYDROLYSIS AND HEAD TWITCH BEHAVIOR.** S. Patel, P.H. Hutson. Merck Sharp and Dohme Research Laboratories, Neuroscience Research Center, Terlings Park, Harlow, Essex. CM20 2Q4, U.K.

Previous studies have demonstrated that the neuropeptide galanin is able to block $5HT_2$ receptor agonist induced head twitch behavior in rat (Ogren and Fuxe, 1989). The $5HT_2$ receptor is known to be coupled to the phosphatidylinositol (PI) cycle, thus in the present study we have examined the interaction between galanin and $5HT_2$ receptor agonist induced PI turnover. Tissue slices of mouse cortex were preincubated (30 min) in the presence of 2μCi [$^3$H]myoinositol and 10mM lithium. They were subsequently incubated in the presence of $5HT_{2A}$ receptor agonists for 45 min before terminating the incubation using a chloroform:methanol (1:2) mixture. Water soluble inositol monophosphates were then isolated by ion-exchange chromatography. 5HT (0.01-1000μM) concentration dependently stimulated PI hydrolysis in mouse cortex (60% over basal) as did the $5HT_2$ receptor agonists (±)2,5-dimethoxy-4-bromoamphetamine (DOB), the iodinated form DOI and mescaline, which stimulated PI hydrolysis to 150 ± 28%, 130 ± 22% and 54 ± 13% respectively of that produced by 10μM 5HT. Preincubation with the $5HT_2$ receptor antagonist ketanserin (0.1-1000μM) concentration dependently blocked the stimulation to 1μM DOB and mescaline, and attenuated the response to 1μM DOI (6.2 ± 6%, 5.4 ±6% and 42 ± 22% respectively at 10μM 5HT at 10μM antagonist). Preincubation with galanin (0.1-10μM) at doses which had no effect on PI hydrolysis alone, blocked the response to 1μM DOB and mescaline, and attenuated the response to 1μM DOI (25 ± 9%, 8 ± 7% and 82 ± 12% respectively of 10μM 5HT response at 10μM galanin).

Mescaline, DOB and DOI dose dependently stimulated head twitch frequency in the mouse (EC50 = 10, 5 and 10mg/kg s.c. respectively). Pretreating animals with ketanserin (0.01-1mg/kg s.c.) blocked head twitch behavior to mescaline and DOB, and attenuated that to DOI. The galanin receptor antagonist galantide (3nmol/5μl) administered immediately before galanin (via the cisterna magna) blocked the inhibition by galanin of mescaline and DOB induced behavior, but did not affect the inhibition by galanin of the response to DOI.

These results confirm and extend the findings in the literature and demonstrate that galanin inhibits $5HT_2$ receptor mediated behavior by inhibiting 5HT receptor agonist induced PI hydrolysis.

Ogren, S.O. and Fuxe, K. (1989), Acta Physiol. Scand. 136, 297-298.

24

**NEUROPEPTIDERGIC MODULATION OF INDIVIDUAL DIFFERENCES IN SUCROSE CONSUMPTION AND AMPHETAMINE-INDUCED RELEASE OF MESOLIMBIC DOPAMINE: CHOLECYSTOKININ AND GALANIN.** T.L. Sills, J.N. Crawley. Section on Behavioral Neuropharmacology, ETB, NIMH, Bethesda, MD.

Rats that consume low amounts of sugar (LOW) respond differently to the psychoactive properties of amphetamine (AMP) than rats that consume high amounts of sugar (HIGH; Sills & Vaccarino, 1991, 1994; Sills et al., 1993). Moreover, HIGH animals were found to express higher levels of AMP-stimulated mesolimbic dopamine (DA) release than LOW animals (Sills & Crawley, submitted). This indicates that intrinsic differences in the functioning of the mesolimbic DA system underlie the expression of individual differences in sugar consumption and responsiveness to AMP.

In addition to DA, the mesolimbic system contains the peptide cholecystokinin (CCK), which has been shown to exert complex modulatory effects on DA transmission and DA-mediated behaviors. Treatment with CCK and $CCK_B$ antagonists differentially affect LOW and HIGH animals under both baseline and AMP-stimulated conditions (Sills & Vaccarino, 1991; Sills and Vaccarino, submitted). These findings indicate that endogenous CCK may play an important role in the expression of individual differences in mesolimbic DA activity and DA-mediated behaviors. In the present study, selective CCK antagonists were assessed for their effects on AMP-stimulated release of mesolimbic DA in LOW and HIGH animals using in vivo microdialysis.

Additionally, galanin was tested for its actions on sugar consumption in LOW versus HIGH sugar consumers. Galanin has a potent stimulatory effect on food intake and evidence indicates that galanin stimulates mesolimbic DA activity (Crawley et al., 1990, 1993; Corwin et al., 1993; Rada et al., 1994). In the present study, galanin increased sugar consumption equally in LOW and HIGH animals. Thus, in contrast to CCK, galanin affects LOW and HIGH animals in a similar manner.